alzheimer's association

Alzheimer's Association
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ALZHEIMER'S TREATMENT STUDY REPORTS THREE YEARS WITH NO DECLINE IN MEMORY AND FUNCTION AT AAIC 2012

Also, Special Session Previews the First Three Prevention Trials in Presymptomatic Alzheimer's

VANCOUVER, July 17, 2012 -- The first report of long-term (three-year) stabilization of Alzheimer's disease symptoms with IVIG (Gammagard, Baxter), including no decline on measures of cognition, memory, daily functioning and mood, was reported today at the Alzheimer's Association International Conference 2012 (AAIC 2012) in Vancouver.

In addition, updates were given on three new presymptomatic Alzheimer's disease treatment trials that are beginning soon or in the planning stages. At an AAIC 2012 Featured Research Session titled "Collaboration for Alzheimer's Prevention: Common Issues Across Presymptomatic Treatment Trials," the principal investigators of the three trials described their current status, followed by a panel discussion.

Disappointing results from recent Alzheimer's clinical trials suggest that we may be testing therapies too late in the process of the disease -- that once dementia symptoms are evident, too much damage has been done to the brain for effective treatment.

"Fortunately, improving detection technologies and updated diagnostic guidelines are enabling the detection of early changes in the brain and subtle cognitive deficits that are consistent with what is now known as presymptomatic (or preclinical) Alzheimer's," said William Thies, PhD, Alzheimer's Association chief medical and scientific officer. "People in this stage of the disease are an ideal population for prevention trials to delay the onset or slow the progression of cognitive decline."

Well-organized and characterized study populations of people with younger-onset genetic Alzheimer's are making possible two of the innovative new studies. What we learn from studying this rare group of people with Alzheimer's – they comprise less than two percent of the total global Alzheimer's population – may provide strong guidance for attacking the much more common late onset sporadic Alzheimer's.

"These four studies are among the most exciting current and upcoming Alzheimer's therapy trials," Thies said.

First report of long-term stabilization of Alzheimer's in 3 year extension of Phase II IVIG trial

Intravenous immunoglobulin★ (IVIG/Gammagard, Baxter) is being studied as an immunotherapy for Alzheimer's. Positive results of a placebo controlled Phase 2 study in mild to moderate Alzheimer's were previously reported. The 24 participants in that study received six months of treatment followed by a 12-month open-label extension where all subjects received IVIG. Several doses were tested.

To evaluate the long term effects of IVIG, participants were offered additional IVIG treatment at a single standardized dose (0.4mg/kg every 2 weeks) for an additional 18 months. Sixteen of the originally enrolled subjects received treatment through month 36, including five originally given placebo and 11 treated with various doses of IVIG.

The researchers found that:

- Study participants who were treated with IVIG 0.4g/kg every two weeks for the full 36 months (n=4) had the best outcome, with no decline on several standard measures of cognition, memory, daily functioning and mood (ADAS-Cog, CGIC, 3MS, ADCS-ADL, NPI, QOL) at the three year endpoint.
- As a group, the 11 participants who received IVIG for the full 36 months had favorable outcomes in terms of their thinking abilities, behavior and daily function.
- The five participants who were initially treated with a placebo and then switched to IVIG declined while on placebo but experienced less rapid decline while receiving a uniform dose of IVIG.

"Alzheimer's disease progresses over many years," said study leader Norman Relkin, MD, PhD, of Weill Cornell Medical College, New York City. "It is crucial that we find effective, long-term treatments."

"This is the first study to report long term stabilization of Alzheimer's symptoms with IVIG. While the small number of participants may limit the reliability of our findings, we are very enthusiastic about the results. A Phase 3 trial is in progress and, in less than one year, we'll have more definitive data on the efficacy of 18 months of IVIG treatment."

> ★ IVIG is a blood product that is administered intravenously. Each dose contains pooled antibodies extracted from the plasma of more than 1,000 blood donors. IVIG is given to immune deficient patients who have decreased or absent antibody production capabilities to prevent infections. It is mainly used in immune deficiencies, autoimmune diseases, and acute infections.

Anti-Amyloid Treatment of Asymptomatic Alzheimer's Disease

The Alzheimer's Disease Cooperative Study (ADCS)★★ has proposed a placebo-controlled, three-year trial in clinically normal older adults with biomarker evidence of Alzheimer's changes in their brains, to be known as the Anti-Amyloid Treatment of Asymptomatic Alzheimer's Disease (A4) trial. The funding application will be reviewed in early July 2012 at the National Institute on Aging, with the hope of starting participant enrollment in mid-2013.

Eligible participants will have normal memory and thinking abilities, age 70+, with evidence of amyloid buildup in their brain shown on a PET scan using an amyloid imaging dye. The primary outcome will be slowing the rate of cognitive decline on a test that probes episodic memory (times, places, associated emotions, and other related knowledge) and executive function (including functions such as planning, problem solving, verbal reasoning, inhibition, and initiation). The researchers are also developing a novel computerized test battery for an exploratory cognitive outcome. Multiple biomarkers, including structural and functional imaging, and spinal fluid assays, will be used as secondary outcomes.

The choice of an experimental treatment for the A4 trial has not yet been finalized. According to the scientists, it will likely be a monoclonal antibody against amyloid with clear evidence of target engagement and adequate safety data.

"This is the optimum time to launch this study because we now have the biomarker measuring tools and experimental drugs to test the hypothesis that reducing amyloid burden in the brain will slow the loss of nerve cells in Alzheimer's, and thereby delay or prevent cognitive decline." said A4 principal investigator Reisa Sperling, MD, of Harvard Medical School and Brigham & Women's Hospital, Boston.

"And, because we're planning to study cognitively normal older adults, the A4 trial will complement the Alzheimer's prevention initiatives conducted in younger-onset genetic Alzheimer's families."

> ** The ADCS was formed in 1991 as a cooperative agreement between the National Institute on Aging and the University of California San Diego. Led by Paul Aisen, MD, the ADCS is a major initiative for Alzheimer's disease clinical studies in the federal government to facilitate the discovery, development and testing of new drugs for Alzheimer's.

The Dominantly Inherited Alzheimer Network – Therapeutic Trials Unit

The Dominantly Inherited Alzheimer Network (DIAN) – Therapeutic Trials Unit*** is preparing to launch prevention trials in people with young-onset genetic Alzheimer's.

> *** The DIAN Study itself is not designed to test any treatments or preventive strategies; rather, it is designed to collect information about the changes in the brain that precede the development of disease symptoms. However, because biochemical changes can be detected and measured many years before symptoms develop, it may be possible for researchers to develop treatments that halt or slow the biological processes that cause those biochemical changes, potentially arresting the disease process before brain function is impaired. The DIAN Therapeutic Trials Unit (DIAN-TTU) was developed to pursue this possibility. The Alzheimer's Association is the lead funder of the project, accounting for 56% of its initial funding, with the DIAN Pharma Consortium, a pioneering consortium of 10 pharmaceutical companies providing the balance.

The DIAN-TTU has developed a novel clinical trial design that may accelerate approval of the best therapeutic treatments for Alzheimer's. The proposed design is a two-stage study to delay, prevent, or restore cognitive loss in people who carry an Alzheimer's gene mutation. The first stage will determine the biological engagement of the drug target and the impact of the drug on Alzheimer's biomarkers. The second stage will determine if there is a cognitive benefit. Three drugs will be tested initially. The trial is expected to start in late 2012 or early 2013.

"Prevention studies are likely to be most successful for those people with the highest risk of Alzheimer's," said study leader Randall Bateman, MD, of Washington University School of Medicine, St. Louis, Missouri.

"People with dominantly inherited Alzheimer's disease develop the same pathologic changes in the brain — amyloid plaques and neurofibrillary tangles — as people who have other forms of the disease, but those changes develop at a younger age. Scientists believe, therefore, that there is significant overlap of the causes and progression in people with dominantly inherited Alzheimer's and other forms of the disease."

According to Bateman, the DIAN study has already confirmed the similarities between dominantly inherited Alzheimer's disease and sporadic Alzheimer's disease cases. Because of this similarity, the researchers believe the results of the DIAN project are likely to be applicable to a broader population affected by Alzheimer's disease.

"Clinical studies in Alzheimer's that is caused by gene mutations are likely to pioneer the way to prevention trials for all forms of the disease," Bateman said.

The Alzheimer's Prevention Initiative

The Alzheimer's Prevention Initiative (API) aims to conduct preclinical Alzheimer's treatment trials of amyloid-modifying treatments in cognitively normal people who, based on their age and genetic background, are at the highest imminent risk of Alzheimer's symptoms. It also aims to establish some of the tools and enrollment registries needed to test promising prevention therapies as quickly as possible. The primary study population is an unusually large kindred near Medellin, Colombia, affected by a genetically-caused form of younger-onset Alzheimer's.

"There is an urgent need to find effective preclinical Alzheimer's treatments to postpone the onset, reduce the risk of, or completely prevent Alzheimer's," said two of the lead investigators, Eric Reiman, MD, and Pierre Tariot, MD, of Banner Alzheimer's Institute, Phoenix, Arizona. "We believe this study group offers a unique opportunity because of its size, shared genetic background, and commitment to the fight against Alzheimer's."

As recently announced, study leaders from the Banner Alzheimer's Institute chose crenezumab (Genentech), a humanized monoclonal antibody against beta amyloid, as the therapeutic agent for this trial. The API trial will test the drug on 300 individuals from the Columbian kindred, and about two dozen people in the U.S., who have younger-onset Alzheimer's-causing gene mutations, but do not yet show symptoms of the disease.

According to Reiman, "The trial will determine whether crenezumab can reduce participants' chances of developing the disabling and irreversible symptoms of Alzheimer's, preserve memory and thinking abilities, and slow the progression of Alzheimer's biomarkers – including the best established brain imaging and cerebrospinal fluid measurements. It is based on the idea that certain treatments may need to be started before the onset of symptoms to have their greatest benefit."

"We feel that it is important to give persons at highest risk access to promising investigational treatments, and to conduct the study in a way that provides the greatest possible benefit to the field" Reiman said.

Similar to the DIAN-TTU, it is hoped that the findings will provide insights and lead to similar studies in people at risk for the more common form of the disease later in life.

About AAIC

The Alzheimer's Association International Conference (AAIC) is the world's largest conference of its kind, bringing together researchers from around the world to report and discuss groundbreaking research and information on the cause, diagnosis, treatment and prevention of Alzheimer's disease and related disorders. As a part of the Alzheimer's Association's research program, AAIC serves as a catalyst for generating new knowledge about dementia and fostering a vital, collegial research community.

About the Alzheimer's Association

The Alzheimer's Association is the world's leading voluntary health organization in Alzheimer care, support and research. Our mission is to eliminate Alzheimer's disease through the advancement of research, to provide and enhance care and support for all affected, and to reduce the risk of dementia through the promotion of brain health. Our vision is a world without Alzheimer's. For more information, visit www.alz.org or call 800-272-3900.

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- Norman Relkin, et al. Three Year Follow-up on the IVIG for Alzheimer's Phase II Study. (Funder: Baxter Healthcare)
- Reisa Sperling, et al. The A4 Trial: Anti-Amyloid Treatment of Asymptomatic Alzheimer's Disease. (Funder: Alzheimer's Disease Cooperative Study, National Institute on Aging)
- Randall Bateman, et al. The Dominantly Inherited Alzheimer's Network Trials: An opportunity to prevent AD. (Funders: National Institutes of Health, Alzheimer's Association, DIAN Pharma Consortium)
- Eric Reiman, et al. The Alzheimer's Prevention Initiative. (Funders: Genentech, Banner Alzheimer's Institute, National Institutes of Health)

P3-381 Tuesday, July 17 / Poster session

Three Year Follow-up on the IVIG for Alzheimer's Phase II Study

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Background: Intravenous Immunoglobulin (IVIG) is under study as an agent for immunotherapy of Alzheimer's Disease (AD). Positive results of a Phase 2 double-blind placebo-controlled study of IVIG for mild to moderate AD were previously reported. The 24 participants in that study underwent 6 months of placebo controlled treatment followed by a 12 month open-label extension in which all subjects received IVIG. To evaluate the long term effects of IVIG, participants were offered additional IVIG treatment at a standardized dose under an IRB-approved extension protocol.

Methods: Subjects who participated in the Phase 2 study and consented to continuation of treatment were given IVIG (Gammagard, Baxter) 0.4g/kg/2 weeks beginning at post-enrollment month 18. Subjects returned for clinical evaluations at 6 months intervals. A battery of cognitive, functional and behavioral measures were administered at each visit. Adverse events were tracked throughout the study.

Results: IVIG treatment was well tolerated. A total of 16 of the originally enrolled subjects received treatment through month 36. This included 5/8 originally treated with placebo, and 11/16 given IVIG at various doses from time of randomization. Subjects who were treated with IVIG 0.4g/kg/2 weeks for the full 36 months had the best outcome, with no decline in ADAS-Cog, CGIC, 3MS, ADCS-ADL, NPI or QOL measures at the 3 year endpoint. In contrast, subjects treated with placebo initially or IVIG at other doses declined significantly.

Conclusions: This is the first study to report long term stabilization of AD symptoms with IVIG treatment over a period of 36 months. Limitations of the study include the small number of participants and the biases inherent in an open label extension study. The GAP Phase 3 trial is currently in progress and will provide pivotal data on the safety and efficacy of 18 months of IVIG treatment of AD.

F3-04
Tuesday, July 17 / AAIC 2012 Featured Research Session, 8:30-10 AM

Collaboration for Alzheimer's Prevention: Common Issues Across Presymptomatic Treatment Trials

Session Description: Among these three groups planning, and preparing to implement, presymptomatic Alzheimer's disease treatment trials, several cross-cutting themes emerge that will be discussed in a 45 minute moderated panel format that includes the speakers as well as international leaders in recruitment, trial design and outcomes, biomarkers, regulatory affairs, and ethics. Examples of these include the following. What are potentially the most informative aspects of the different designs, and where might we go next? What are the key merits of different enrichment techniques? What has been learned about the most appropriate processes for and means of selecting interventions , and how can they be improved upon? How about funding? What have we learned about the essential elements of clinical outcomes in people who do not have cognitive impairment at enrollment? What are the best current ideas about how to use imaging and fluid biomarkers, and how to study their predictive, prognostic, and correlative values? What pathways for possible regulatory approval are emerging? Are we addressing the critical ethical issues and anticipating future themes? How do we engage the public, ranging from education regarding the need for prevention trials and assuring timely recruitment, particularly of minority groups? Are we doing everything possible to achieve critical consensus from the relevant stakeholder groups, including patient and family advocates, scientists, regulatory officials, public policy experts, and government leaders? How do we assure that lessons learned are generalized as quickly as possible, and access to assets and data collected following completion of the trial?

F3-04-01
Tuesday, July 17 / AAIC 2012 Featured Research Session, 8:30-10 AM

The A4 Trial: Anti-Amyloid Treatment of Asymptomatic Alzheimer's Disease

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Background: Disappointing results from recent clinical trials and transgenic animal experiments suggest that we may be testing anti-Ab therapies much too late in the pathophysiological process of Alzheimer's disease (AD). Converging data from PET amyloid imaging, cerebrospinal fluid studies, and large autopsy series suggest that approximately one-third of clinically normal older individuals harbor a substantial burden of cerebral amyloid-b. These amyloid-positive "normals" demonstrate evidence of functional and structural imaging abnormalities, elevation of CSF tau, and subtle cognitive deficits, consistent with the preclinical stages of AD, and represent an ideal population for a large secondary prevention effort to slow cognitive decline.

Methods: The Alzheimer's Disease Cooperative Study (ADCS) is proposing a placebo-controlled, 3-year trial in clinically normal older individuals with biomarker evidence of AD pathology. The primary outcome will be slowing the rate of decline on a cognitive composite, with multiple biomarkers as secondary outcomes. Eligible subjects will be clinically normal (CDR 0, MMSE 27-30), over age 70, and will have evidence of amyloid-positivity on PET amyloid imaging. The choice of treatment has not yet been finalized, but will be a monoclonal antibody with clear evidence of target engagement and adequate safety data to support a 3-year trial.

Results: Analyses using available data from the Alzheimer's Disease Neuroimaging Initiative and Australian Imaging Biomarkers Lifestyle study consistently demonstrate evidence of an increased rate of cognitive decline in amyloid-positive normals, and that approximately n=500 subjects per arm will yield adequate power to detect a 25-35% treatment-related decrease in the rate of cognitive decline. We will also include a natural history arm of 500 amyloid-negative individuals to investigate the specific pattern of "amyloid-related" decline and to develop more sensitive outcome measures to improve the efficiency of future secondary prevention trials in preclinical AD.

Conclusions: The A4 trial will provide complementary information to the prevention initiatives being planned in genetic-risk cohorts. Although amyloid-b may be only one of several pathogenic factors in the elderly population, we now have the biomarker tools and biologically active compounds to test the hypothesis that altering "upstream" amyloid burden will impact "downstream" neurodegeneration and delay or prevent cognitive decline.

F3-04-02
Tuesday, July 17 / AAIC 2012 Featured Research Session, 8:30-10 AM

The Dominantly Inherited Alzheimer's Network Trials: An opportunity to prevent AD

Randall Bateman, John Morris
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Background: Prevention studies are likely to be most successful for those with the highest risk of AD. Autsomal dominant AD accounts for less than 1% of all AD, but has 100% risk and usually occurs in the third to fifth decade of life. In 2008, the NIH funded the establishment of the Dominantly Inherited Alzheimer Network (DIAN, U01AG032438, JC Morris, PI; www.dian-info.org), an international network of leading research centers to investigate AD caused by mutations. The DIAN is the largest and most extensive worldwide network for mutation Alzheimer's research. In collaboration with other prevention initiatives, DIAN is preparing to launch the first prevention trials for autosomal dominant AD.

Methods: Measurements to track disease progression using established clinical, cognitive, imaging and biomarker methods have been performed. The results from the study demonstrate the feasibility and promise of performing prevention studies in the DIAN population. In 2011, the DIAN Therapeutic Trials Unit (TTU) was established with funding from the Alzheimer's Association and a consortium of ten pharmaceutical companies (the DIAN Pharma Consortium). The purpose of the DIAN TTU is to direct the design and management of prevention and interventional trials of DIAN participants.

Results: A sequence of biomarker changes reveal a cascade of events beginning 10-20 years before the first symptoms of AD are manifest. The proposed design for the DIAN prevention trials is a two-phase study to delay, prevent, or restore cognitive loss in AD mutation carriers. The first phase will determine the biological engagement of the drug target and impact on biomarkers of neurodegeneration with imaging, cerebrospinal fluid, and other biomarkers. The second phase will determine if there is a cognitive benefit of treatment.

Conclusions: Because the clinical and pathological phenotypes of dominantly inherited AD appear similar to those for the far more common late-onset "sporadic" AD, the nature and sequence of brain changes in early-onset AD are also likely relevant for late-onset AD. Clinical studies in AD caused by gene mutations are likely to pioneer the way to prevention trials for all forms of AD. The scientific knowledge gained from secondary prevention trials is likely to inform about the cause of AD, validate biomarkers to accelerate treatment development, and determine the effects of treating AD early.

F3-04-03
Tuesday, July 17 / AAIC 2012 Featured Research Session, 8:30-10 AM

The Alzheimer's Prevention Initiative

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Background: There is an urgent need to find demonstrably effective presymptomatic Alzheimer's disease (AD) treatments, those interventions intended to postpone the onset, reduce the risk of, or completely prevent AD symptoms. The Alzheimer's Prevention Initiative (API) aims to conduct presymptomatic AD treatment trials of amyloid-modifying treatments in cognitively normal people, who based on their age and genetic background, are at the highest imminent risk of AD symptoms; to relate a treatment's biomarker effects to clinical outcome; to provide a best test of the amyloid hypothesis; to give persons at highest risk access to promising investigational treatments; to provide exceptionally large Alzheimer's Prevention registries for these and other presymptomatic trials; and to complement, support and benefit from other initiatives.

Methods: The API includes a) a planned presymptomatic AD treatment/biomarker development/nested cohort trial in cognitively normal early-onset AD-causing mutation carriers within 15 years of their estimated age at clinical onset, including PS1 E280A mutation carriers from the world's largest kindred in Antioquia, Colombia; b) a proposed presymptomatic AD treatment/biomarker development trial in cognitively normal APOE Îµ4 homozygotes and heterozygotes; c) an exceptionally large early-onset AD prevention registry in the PS1 E280A kindred; and d) development of an exceptionally large internet-based Alzheimer's Prevention Registry to support the entire research community.

Results: We continue to characterize the preclinical trajectory of early-onset and late-onset AD in our PS1 E280A and APOE cohorts, establish a composite cognitive endpoint with improved power to track evaluate presymptomatic AD treatments; estimated presymptomatic trial sample sizes using amyloid PET, FDG PET, MRI, CSF and cognitive endpoints, vet treatment options for these and other trials, engage a large number of academic, industry and regulatory stakeholders; launch our registries; and prepare for our first presymptomatic trial.

Conclusions: We are excited about our progress, plans, current timelines and the chance to work with other researchers, programs, and stakeholders. Together, we have a chance to set the stage of a new era in AD prevention research, develop the resources, biomarker endpoints, and accelerated regulatory approval pathway needed to rapidly evaluate the range of promising presymptomatic treatments, and find ones that work as soon as possible.

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